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Scientists discover new cause of Alzheimer's, vascular dementia

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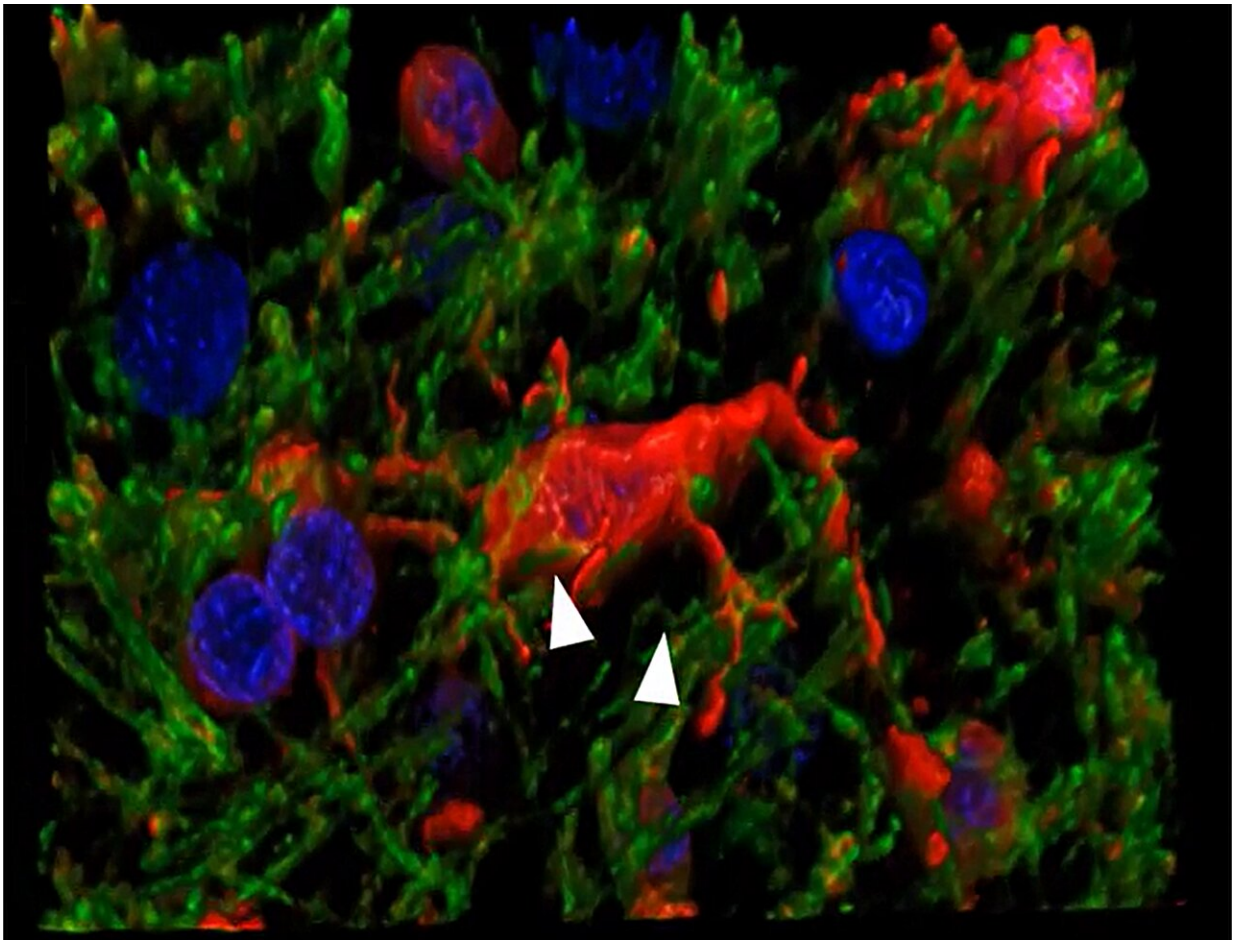


Credit: *Annals of Neurology* (2023). DOI: 10.1002/ana.26770

Researchers have discovered a new avenue of cell death in Alzheimer's

disease and vascular dementia.

A new study, led by scientists at Oregon Health & Science University and published in the journal *Annals of Neurology*, reveals for the first time that a form of cell death known as ferroptosis—caused by a buildup of iron in cells—destroys microglia cells, a type of cell involved in the brain's immune response, in cases of Alzheimer's and vascular dementia.

The researchers conducted the study examining post-mortem human brain tissue of patients with dementia.

"This is a major finding," said senior author Stephen Back, M.D., Ph.D., a neuroscientist and professor of pediatrics in the OHSU School of Medicine.

Back has long studied myelin, the insulation-like protective sheath covering nerve fibers in the brain, including delays in forming myelin in premature infants. The new research extends that line of work by uncovering a cascading form of neurodegeneration triggered by deterioration of myelin. They made the discovery using a novel technique developed by the study's lead author Philip Adeniyi, Ph.D., a postdoctoral researcher in Back's laboratory.

The researchers discovered that microglia degenerates in the white matter of the brain of patients with Alzheimer's and vascular dementia.

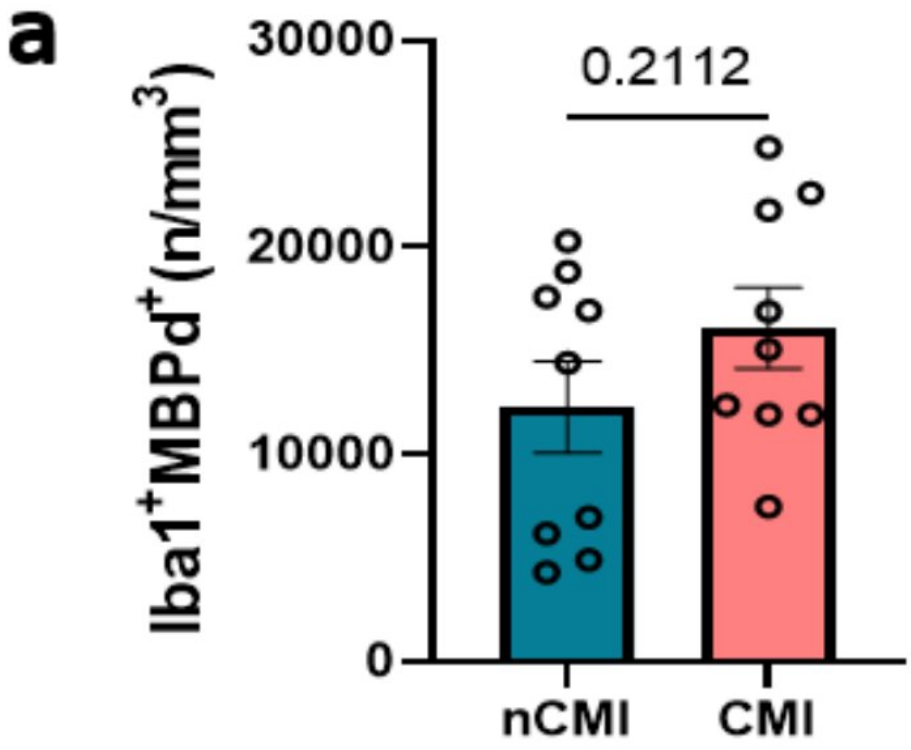
Microglia are resident cells in the brain normally involved in clearing cellular debris as part of the body's immune system. When myelin is damaged, microglia swarm in to clear the debris. In the new study, researchers found that microglia themselves are destroyed by the act of clearing iron-rich myelin—a form of cell death known as ferroptosis.

Given the intense scientific focus on the underlying cause of dementia in

older adults, Back called it amazing that researchers hadn't made the connection to ferroptosis until now.

"We've missed a major form of cell death in Alzheimer's disease and vascular dementia," Back said. "We hadn't been giving much attention to microglia as vulnerable cells, and white matter injury in the brain has received relatively little attention."

Co-author Kiera Degener-O'Brien, M.D., initially discovered the degeneration of microglia in tissue samples, Back said. Adeniyi subsequently developed a novel immunofluorescence technique to determine that iron toxicity was causing microglial degeneration in the brain. This was likely a result of the fact that the fragments of myelin are themselves rich in iron, Back said.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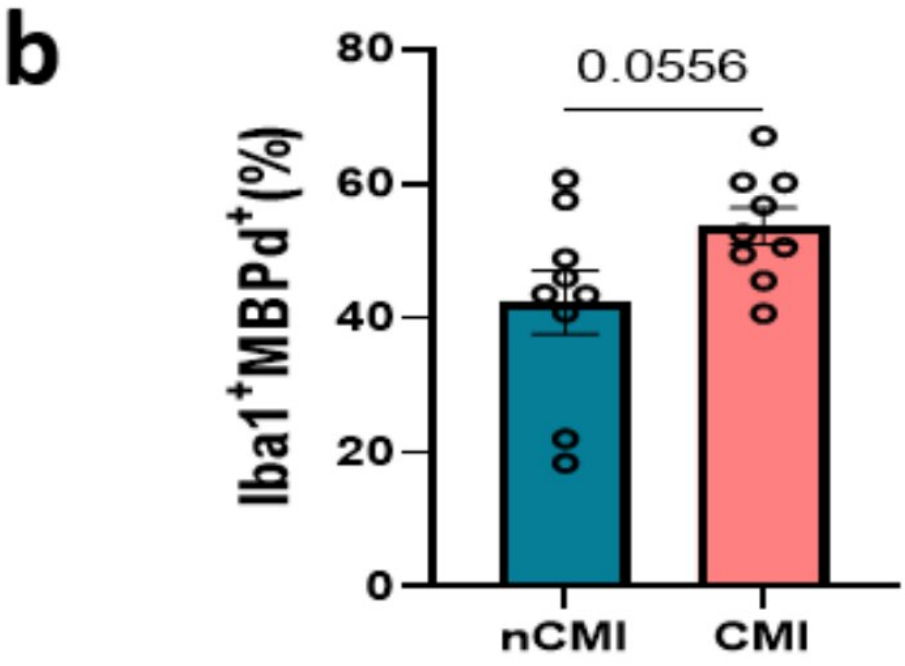
b
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40
20
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Iba1+MBPd+(%)
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nCMI
CMI

The density (a) and percentage (b) of Iba1$^+$ DM containing myelin debris in CMI and nCMI cases were similar and displayed no significant differences. Credit: *Annals of Neurology* (2023). DOI: 10.1002/ana.26770

In effect, the immune cells were dying in the line of duty.

"Everyone knows that microglia are activated to mediate inflammation," Back said. "But no one knew that they were dying in such large numbers. It's just amazing that we missed this until now."

The study finds that the cascading effect of degenerating microglia appears to be a mechanism in advancing cognitive decline in Alzheimer's disease and vascular dementia, Back said. He expects pharmaceutical companies will use this new finding to develop compounds focused on reducing microglial degeneration in the brain.

"That's where the field will go next," he said. "A discovery like ours will stimulate a lot of excitement in the pharmaceutical industry to develop therapeutically important compounds."

He said the underlying cause initiating the cycle of decline likely relates to repeated episodes of low blood flow and oxygen delivery to the brain over time due to acute stroke or chronic conditions such as hypertension and diabetes.

"Dementia is a process that goes on for years and years," Back said. "We have to tackle this from the early days to have an impact so that it doesn't spin out of control."

More information: Philip A. Adeniyi et al, Ferroptosis of microglia in aging human white matter injury, *Annals of Neurology* (2023). DOI: 10.1002/ana.26770